

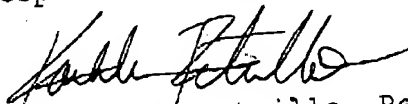
BXTD 9005
ELX-5704 (US)
PATENT

REMARKS

- * Attached hereto is a marked-up version of the changes made
- * by this amendment. The attached pages are captioned "Version With Markings to Show Changes Made."

The amendments are presented to correct two incomplete sentences that were discovered in the application. Applicant believes that the amendments do not introduce new matter. However, if the Examiner decides otherwise, applicant will delete such amendment to retain benefit of its earliest priority date.

Respectfully submitted,


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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph beginning at page 15, line 4 has been amended as follows:

As mentioned in above, erythropoietins prepared from different DNA (genomic or cDNA) and/or in different cell lines have different glycosylation patterns and other attributes resulting in glycoproteins with differing biological activities. In the case of Epoetin Omega, broad peak fractions selected from a final isoelectric purification step, in vivo assay results using a polycythemic mouse assay typically show a range from about 40,000 to about 65,000 IU/mg. More narrowly selected peak fractions have an in vivo activity in the range of 90,000 IU to 120,000 IU per mg. For Epoetin Alfa, in vivo activity of pharmaceutical preparations typically are in the range fo about 110,000 IU per mg. Pharmaceutical preparations are tested in a quality assurance / quality control process using the polycythemic mouse assay before being released for human use. For example, under the conditions of an exhypoxic polycythemic mice assay (see, Nature (1961) 191:1069-1087), values ranging from about 40,000 to about 65,000 U/mg are observed for Epoetin Omega. Radioimmunoassay results indicate an in vitro biological activity in the range of about 200,000 to about 240,000 U/mg for Epoetin Omega. Purified urinary EPO has been reported to have an in vivo activity from about 45,000 IU upwards to about 75,000 or more per mg. In addition, there are likely corresponding differences in the secondary or tertiary structures of the recombinant Erythropoietins (i.e., protein structure/folding) as well as the established differences in carbohydrate composition and bonding strength thereof, as well as stability of the various

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glycoproteins even though the primary protein sequence may be identical. Each known form of recombinant erythropoietin is a glycoprotein having a myriad of complex carbohydrate chains that include sugars that are N-linked to amino residues and/or O-linked to hydroxy residues. However, the content amount, number, position, bond strength, structure and composition of the carbohydrate linkages differ between the different recombinant erythropoietins and between urinary human erythropoietin. The structure and composition of Epoetin Omega carbohydrate residues has been described for example, by Nimtz et al. *Eur. J. Biochem.* 213:39, (1993); Tsuda et al. *Eur. J. Biochem.* 188:405, (1990); and Sytkowski et al., *Biochem. Biophys. Res. Comm.* 176:698, (1988) each of which are incorporated herein by reference in their entirety.

The paragraph beginning at page 47, line 3 has been amended as follows:

Epoetin Omega is typically formulated in doses of 2000 or 4000 IU/ml with a pharmaceutically acceptable carrier or diluent for subcutaneous (s.c) or intravenous (i.v) injection. An example carrier or diluent in a 1 ml volume might include: sodium chloride (NaCl) 8.18 mg, monobasic sodium phosphate ($\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$) 1.56 mg, sodium hydroxide (NaOH) to pH 7.2, and human serum albumin 1.0 mg.